

# ULTRASONIC DIAGNOSTIC IMAGING WITH HARMONIC CONTRAST AGENTS

This invention relates to ultrasonic diagnosis and imaging of the body with ultrasonic contrast agents and, in particular, to new methods and apparatus for ultrasonically detecting and imaging with contrast agents.

Ultrasonic diagnostic imaging systems are capable of imaging and measuring the physiology within the body in a completely noninvasive manner. Ultrasonic waves are transmitted into the body from the surface of the skin and are reflected from tissue and cells within the body. The reflected echoes are received by an ultrasonic transducer and processed to produce an image or measurement of blood flow. Diagnosis is thereby possible with no intervention into the body of the patient.

However materials known as ultrasonic contrast agents can be introduced into the body to enhance ultrasonic diagnosis. Contrast agents are substances which will strongly interact with ultrasonic waves, returning echoes which may be clearly distinguished from those returned by blood and tissue. One class of substances which has been found to be especially useful as an ultrasonic contrast agent is gases, in the form of tiny bubbles called microbubbles. Microbubbles present a significant acoustic impedance mismatch in comparison to tissue and fluids, and nonlinear behavior in certain acoustic fields which is readily detectable through special ultrasonic processing. In order to infuse bubbles into the body so that they will survive passage through the pulmonary system and circulate throughout the vascular system, gases have been stabilized in solutions in the form of tiny microbubbles. Microbubble contrast agents are useful for imaging the body's vascular system, for instance, as the contrast agent can be injected into the bloodstream and will pass through the veins and arteries of the body with the blood supply until filtered from the blood stream in the lungs, kidneys and liver.

One property of microbubble contrast agents currently under investigation is harmonic response. These harmonic contrast agents exhibit significant, detectable responses at frequencies which are harmonics of the transmitted ultrasonic frequency. This property is useful for clutter rejection of the received signals. When the transmitted frequency band is used as the received frequency band, echoes will be returned from the microbubbles, but also from surrounding tissue, the latter comprising clutter in the received echo signals. But with harmonic contrast agents, reception occurs at harmonic frequencies, where fundamental band clutter from tissue is ignored. Since tissue generally reflects very minimal harmonic components, the received harmonic band enables the microbubble echoes to be received with a high signal to noise ratio.

In accordance with the principles of present invention, a technique is provided for the detection and imaging of harmonic ultrasonic contrast agents. The harmonic contrast agent is insonified by alternate polarity transmitted pulses, and the echo signals received from the transmitted pulses are combined. The result is a suppression of harmonic components of the transmitted ultrasonic waves and the elimination of clutter.

In the drawings:

FIG. 1 illustrates in block diagram form apparatus constructed in accordance with the present invention which provides performance advantages for harmonic contrast agent detection;

FIGS. 2 and 3 illustrate passband characteristics used to explain the performance of the embodiment of FIG. 1;

FIGS. 4a and 4b illustrates the alternate polarity pulsing of harmonic contrast agents; and

FIGS. 5a-5c illustrate nonlinear response waveforms produced by alternate polarity acquisition of contrast agent echoes.

Referring to FIG. 1, an ultrasonic diagnostic system for use with harmonic contrast agents in accordance with the present invention is shown in block diagram form. In this system an array transducer 112 of a probe 110 transmits ultrasonic energy and receives echoes returned in response to this transmission. The response characteristic of the transducer can exhibit two passbands, one around the central transmit frequency and another about the center of the received passband. For imaging harmonic contrast agents, a broadband transducer having a passband encompassing both the transmit and receive passbands is preferred. The transducer may be manufactured and tuned to exhibit a response characteristic as shown in FIG. 2, in which the lower hump 60 of the response characteristic is centered about the center transmit frequency  $f_r$  and the upper hump 62 is centered about the center frequency  $f_r$  of the response passband. The transducer response characteristic of FIG. 3 is preferred, however, as the single dominant characteristic 64 allows the probe to be suitable for both harmonic contrast imaging and imaging without harmonic contrast agents. The characteristic 64 encompasses the central transmit frequency  $f_r$  and also the harmonic receive passband bounded between frequencies  $f_L$  and  $f_c$ , and centered about frequency  $f_r$ . A typical harmonic contrast agent can have a response such that transmission about a central transmit frequency of 1.7 MHz will result in harmonic returning echo signals about a frequency of 3.4 MHz. A bandwidth characteristic 64 of approximately 2 MHz would be suitable for these harmonic frequencies.

In FIG. 1 a central controller 120 provides a control signal  $f_r$  to a transmit frequency control circuit or pulser 121 to control the center frequency and time of transmission of the transmitted ultrasonic energy. The transmit frequency control circuit pulses the elements of the transducer array 112 by means of a transmit/receive switch 114.

Echoes received by the transducer array 112 are coupled through the T/R switch 114 and digitized by analog to digital converters 115. The sampling frequency  $f_s$  of the A/D converters 115 is controlled by the central controller. The desired sampling rate dictated by sampling theory is at least twice the highest frequency  $f_c$  of the received passband and, for the preceding exemplary frequencies, might be on the order of at least 8 MHz. Sampling rates higher than the minimum requirement are also desirable.

The echo signal samples from the individual transducer elements are delayed and summed by a beamformer 116 to form coherent echo signals. The digital coherent echo signals are then filtered by a digital filter 118. In this embodiment, the transmit frequency  $f_r$  is not tied to the receiver, and hence the receiver is free to receive a band of frequencies which is separate from the transmitted band. The digital filter 118 bandpass filters the signals in the passband bounded by frequencies  $f_L$  and  $f_c$  in FIG. 3, and can also shift the frequency band to a lower or baseband frequency range. The digital filter could be a filter with a 1 MHz passband and a center frequency of 3.4 MHz in the above example. A preferred digital filter is a parallel arrangement of serially coupled multipliers and accumulators. This arrangement is controlled by the central controller 120, which provides multiplier weights and decimation control which control characteristics of the digital filter. Preferably the arrangement is controlled to operate as a finite impulse response (FIR) filter, and performs both filtering and decimation.

Filtered echo signals from tissue, generally filtered by a passband centered about or demodulated from the transmit frequency, are coupled to a B mode processor 37 for conventional B mode processing. Filtered echo signals of the harmonic contrast agent passband are coupled to a contrast signal detector 128 which performs pulse to pulse summation or integration of temporally discrete echoes from a given spatial location, amplitude or envelope detects the combined signals. Simple two pulse summation of the form  $P_1 + P_2$  may be employed where  $P_1$  represents the echoes received following one pulse and  $P_2$  represents the echoes received following another pulse. The combination of echoes from consecutive pulses may, if desired, be performed before the digital filter 118 rather than after, the decision being a matter of choice of system design.

The filtered echo signals from the digital filter 118 are also coupled to a Doppler processor 130 for conventional Doppler processing to produce velocity and power Doppler signals. The outputs of these processors are coupled to a 3D image rendering processor 132 for the rendering of three dimensional images, which are stored in a 3D image memory 134. Three dimensional rendering may be performed as described in U.S. patent application Ser. No. 08/638,710, and in U.S. Pat. Nos. 5,474,073 and 5,485,842, the latter two patents illustrating three dimensional power Doppler ultrasonic imaging techniques. The signals from the contrast signal detector 128, the processors 37 and 130, and the three dimensional image signals are coupled to a video processor 140 where they may be selected for display on an image display 50 as dictated by user selection. The video processor preferably includes persistence processing, whereby momentary intensity peaks of detected contrast agents can be sustained in the image. One technique for providing persistence is through frame averaging, whereby new image frames are combined with previous frame information on a spatial basis. The combination can be done by weighting the contributions of the old and new frame information and the frame information can be combined in a recursive manner; that is, old frame information is fed back for combining with new frame information. A preferred persistence technique is the fast attack, slow decay technique described in U.S. Pat. No. 5,215,094, which can be applied to both Doppler and contrast agent images.

The apparatus of FIG. 1 performs alternate polarity pulse transmission as illustrated in FIGS. 4a and 4b. In the first transmission of FIG. 4a, the central controller 120 provides a first polarity control signal  $f_{r1}$  to the pulser 121, which drives the transducer elements 112 to transmit a first polarity pulse 20. For the second transmission of FIG. 4b, the central controller 120 provides a second polarity control signal  $f_{r2}$  to the pulser 121, which drives the transducer elements 112 to transmit a second polarity pulse 22.

The echoes received from microbubbles in response to these alternate polarity transmissions are shown in FIGS. 5a and 5b. FIG. 5a illustrates an echo waveform 310 received from the first pulsing of a microbubble contrast agent. The nonuniform amplitudes on either side of the zero reference level illustrate nonlinear reflexive action of microbubbles in the presence of acoustic waves, as the microbubbles nonlinearly compress and expand. The echo waveform of 310 FIG. 5a results from transmission of an ultrasonic pulse exhibiting a first polarity.

Following transmission of the ultrasonic pulse exhibiting the opposite polarity, the echo waveform 312 of FIG. 5b results. This waveform is similarly nonlinear, but out of phase with the first waveform due to the change in pulse polarity. When the two waveforms are combined, a har-

monic response is obtained, as shown in FIG. 5c. The highly nonlinear waveform of FIG. 5c is readily detected, causing the system to become highly sensitive to the contrast agent which produced the nonlinear echo responses.

A mathematical analysis of this effect and response is as follows. To detect the harmonic response of microbubbles, the harmonic component in the incident pressure wave must be suppressed. Based on the analytical solution of the dynamic motion of microbubbles, the primary component of the backscattering pressure magnitude is linearly proportional to the incident pressure and the harmonic component is quadratically proportional to the incident pressure  $p$ , or  $p_s(\omega)\alpha p$ , and  $p_s(2\omega)\alpha p^2$ . Thus, neglecting the higher order terms, one may write the backscattering pressure magnitude  $p_B(\omega)$  from a microbubble in a generic form

$$p_B(\omega) = k_1(\omega)p + k_2(\omega)p^2 \quad (1)$$

where  $k_1$  and  $k_2$  are parametrically related to the acoustic properties of the microbubble such as size, viscosity, surface tension, ambient pressure, etc.

Now assume that the microbubble is excited by two narrow band signals at different times but with the same magnitude  $p$  and at the same frequency  $\omega$ , but with opposite polarity:  $p_{i1} = p \cos \omega t$  and  $p_{i2} = -p \cos \omega t$ . Then the backscattered pressure wave from  $p_{i1} = p \cos \omega t$  is

$$p_{B1}(\omega, t) = k_1(\omega, t)p + k_2(\omega, t)p^2 \quad (2)$$

and from  $p_{i2} = -p \cos \omega t$  is

$$p_{B2}(\omega, t + \delta t) = k_1(\omega, t + \delta t)p + k_2(\omega, t + \delta t)p^2 \quad (3)$$

Then the total backscattered pressure magnitude may be obtained by summing Equations (2) and (3).

$$\begin{aligned} S &= p_{B1} + p_{B2} = (k_1(\omega, t) - k_1(\omega, t + \delta t))p + (k_2(\omega, t) + k_2(\omega, t + \delta t))p^2 \\ &\approx 2k_2(\omega)p^2 \end{aligned} \quad (4)$$

Equation (4) shows that the primary component is eliminated if  $k_1(\omega)$  and  $k_2(\omega)$  do not change substantially in the time duration  $\delta t$ , where  $\delta t$  is small.

Assume the backscattering from microbubbles is quasi-stationary over  $T$ , where  $T$  is the pulse repetition interval. Therefore, the average nonlinear acoustic properties are not changed over time  $T$ , or

$$E\{k_1(\omega, t)\} \approx E\{k_1(\omega, t + T)\}$$

and

$$E\{k_2(\omega, t)\} \approx E\{k_2(\omega, t + T)\}.$$

The relationship of Equation (4) will hold by summing the pulse echoes from two pulses which are time-diverse in  $T$ . The quasi-stationary assumption is valid for slow perfused flow, such as myocardial perfusion.

When the bandwidth of the incident pressure wave is wide, the wideband excitation wave  $P(t)$  may be represented by a Fourier series

$$P(t) = \sum_i A_i(\omega_i) \cos \omega_i t$$

Thus the backscattered pressure magnitude of the microbubbles from  $P(t)$  may be written as

$$P_{B1} = \sum_i k_1(\omega_i) A(\omega_i) + \sum_i k_2(\omega_i) A^2(\omega_i) \quad (5)$$

and the backscattered pressure magnitude of the microbubbles from  $-P(t)$  may be written as 5

$$P_{B2} = - \sum_i k_1(\omega_i) A(\omega_i) + \sum_i k_2(\omega_i) A^2(\omega_i) \quad (6)$$

Summing Equations (5) and (6), one may obtain 10

$$S = P_{B1} + P_{B2} = 2 \sum_i k_2(\omega_i) A^2(\omega_i) \quad (7)$$

Again, the harmonic component is extracted and the primary component is eliminated.

Let us assume the nonlinearity in tissue is negligible. 15  
Since the backscattered pressure in a linear medium is linearly proportional to the incident pressure wave, the polarity of the backscattered wave will be changed as the polarity of the incident pressure wave is changed. Assuming 20  
the tissue is relatively stationary during the period of two consecutive pulses, summing the pulse echoes from consecutive pulses with opposite polarity will cancel the echo response from tissue. Thus, tissue clutter will be suppressed.

The concept of summing the pulse echoes from two 25  
pulses of opposite polarity may be generalized into processing echoes from multiple pulses with alternate polarity to maximize the sensitivity and minimize the variance, assuming the tissue is stationary during the pulsing interval. Let the pulse sequence be 30

$$P = \{p \ -p \ p \ -p \ p \ -p \ \dots \ -p \ p\}$$

and the pulse echoes be

$$E = \{E_1 \ E_2 \ E_3 \ E_4 \ E_5 \ E_6 \ \dots \ E_n\}$$

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$$S = \sum_{j=1}^{n-1} E_j + E_{j+1} = 2(n-1) \sum_i k_2(\omega_i) A^2(\omega_i)$$

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5. A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

5 transmitting at least three ultrasonic pulses into the body which exhibit first and second characteristics that cause a reduction in the linear echo response when echoes received in response to such pulses are combined;

10 receiving echoes in response to said ultrasonic pulses; and

combining said echoes to produce a nonlinear response.

15 6. The method of Claim 5, wherein said step of receiving echoes comprises receiving echoes from a given location in the body.

20 7. The method of Claim 5, wherein said ultrasonic pulses are transmitted in a sequence in which said first and second characteristics are alternated from pulse to pulse.

25 8. The method of Claim 5, wherein said step of combining comprises summing pairs of echoes.

30 9. The method of Claim 5, wherein said ultrasonic pulses are transmitted in a sequence in which said first and second characteristics are alternated from pulse to pulse; and  
wherein said step of combining comprises summing pairs of echoes from successive pulses.

35 10. The method of Claim 5, wherein said first and second characteristics comprise first and second

polarities.

11. The method of Claim 10, wherein said pulse sequence is of the form {p -p p ...}.

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12. The method of Claim 5, wherein said step of combining produces a result which is substantially equal to 
$$S = \sum_{j=1}^{n-1} (E_j + E_{j+1}) \cdot$$

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13. The method of Claim 12, wherein the number of ultrasonic pulses which is transmitted is three.

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14. A method of ultrasonically detecting the nonlinear ultrasonic response of a medium inside the body comprising the steps of:

transmitting a first ultrasonic pulse to said medium to cause a first echo response;

transmitting a second ultrasonic pulse to said medium to cause a second echo response;

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transmitting a third ultrasonic pulse to said medium to cause a third echo response which is substantially the same as said first echo response; and

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combining said first, second and third echo responses to produce a nonlinear response.

15. The method of Claim 14, wherein said pulse sequence is of the form {p -p p}.

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16. The method of Claim 14, wherein said step of combining produces a result which is substantially equal to 
$$S = \sum_{j=1}^{n-1} (E_j + E_{j+1}) \cdot$$



17. A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

5 transmitting at least three ultrasonic pulses into the body in a sequence which is of the form {p -p p -p ... -p p};  
receiving echoes in response to said ultrasonic pulses which comprise a sequence of the form {E<sub>1</sub> E<sub>2</sub> E<sub>3</sub> E<sub>4</sub> ... E<sub>n-1</sub> E<sub>n</sub>}; and  
10 accumulating said echoes to produce a nonlinear response.

18. The method of Claim 17, wherein said step of accumulating comprises accumulating pairs of  
15 consecutive echoes.

19. The method of Claim 17, wherein said step of accumulating produces a result which is  
substantially equal to 
$$S = \sum_{j=1}^{n-1} (E_j + E_{j+1}) \div$$
  
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20. A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:  
transmitting a sequence of at least three  
25 ultrasonic pulses into the body which exhibit a transmit characteristic which alternates from pulse to pulse;  
receiving echoes in response to said ultrasonic pulses; and  
30 combining said echoes to produce a nonlinear response.

21. The method of Claim 20, wherein said pulses are transmitted to a given location in the body; and

wherein said step of combining reduces the primary component of said echoes and produces a harmonic response.

5           22. The method of Claim 20, wherein said step of transmitting produces a sequence of echoes relating to a given location in the body in which the phase of the primary component of echoes produced by one transmit characteristic is out of phase with the  
10 phase of the primary component of echoes produced by the alternate transmit characteristic.

15           23. The method of Claim 22, wherein said step of combining reduces the primary component of the combined echoes and produces a harmonic response.

20           24. The method of Claim 23, wherein said transmit characteristic is a polarity differential from pulse to pulse.

25. The method of Claim 23, wherein said transmit characteristic is a phase differential from pulse to pulse.

Reissue Application of: Juin-Jet Hwang and David  
Hope Simpson

Title: ULTRASONIC DIAGNOSTIC IMAGING WITH HARMONIC  
CONTRAST AGENTS

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#### ABSTRACT

Apparatus and methods are disclosed for the detection and imaging of ultrasonic harmonic contrast agents. The harmonic echo effect is detected through alternate polarity acquisition of harmonic contrast agent effects, which provides the benefits of suppressing the harmonic components of the transmitted signal while eliminating clutter.

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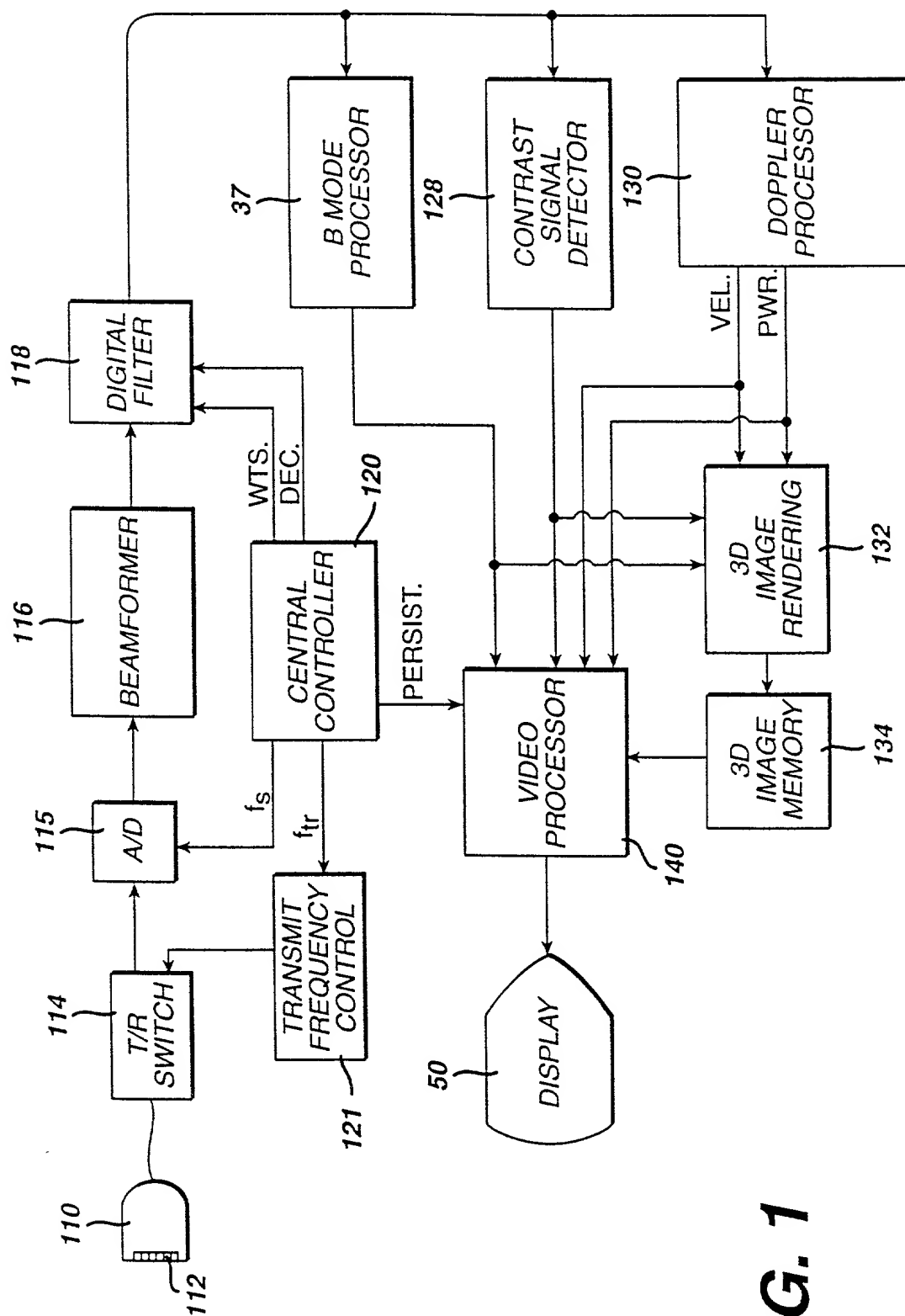


FIG. 1

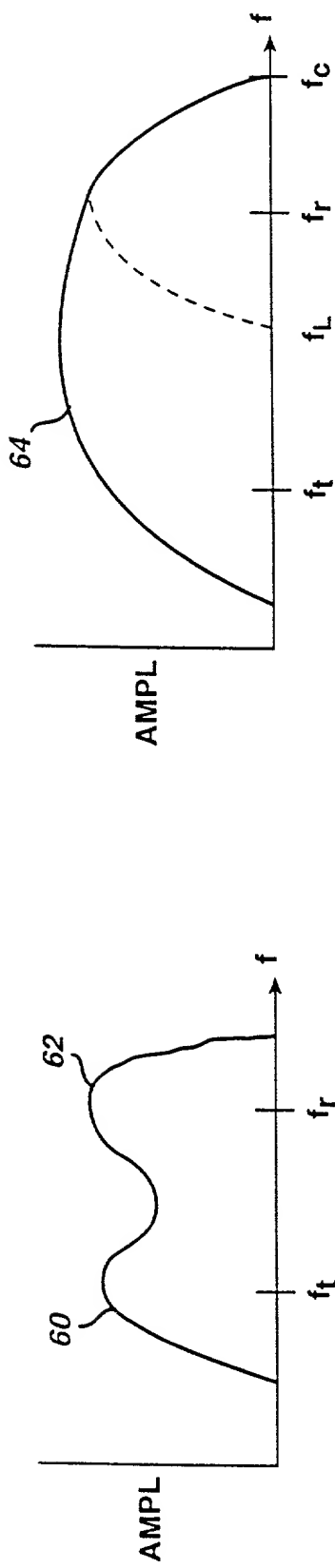


FIG. 2

FIG. 3

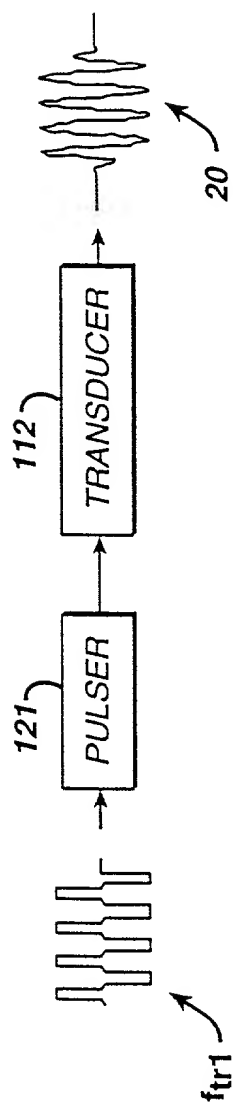


FIG. 4a

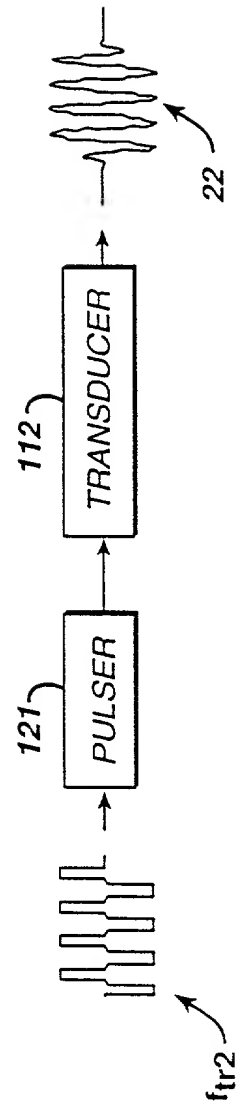
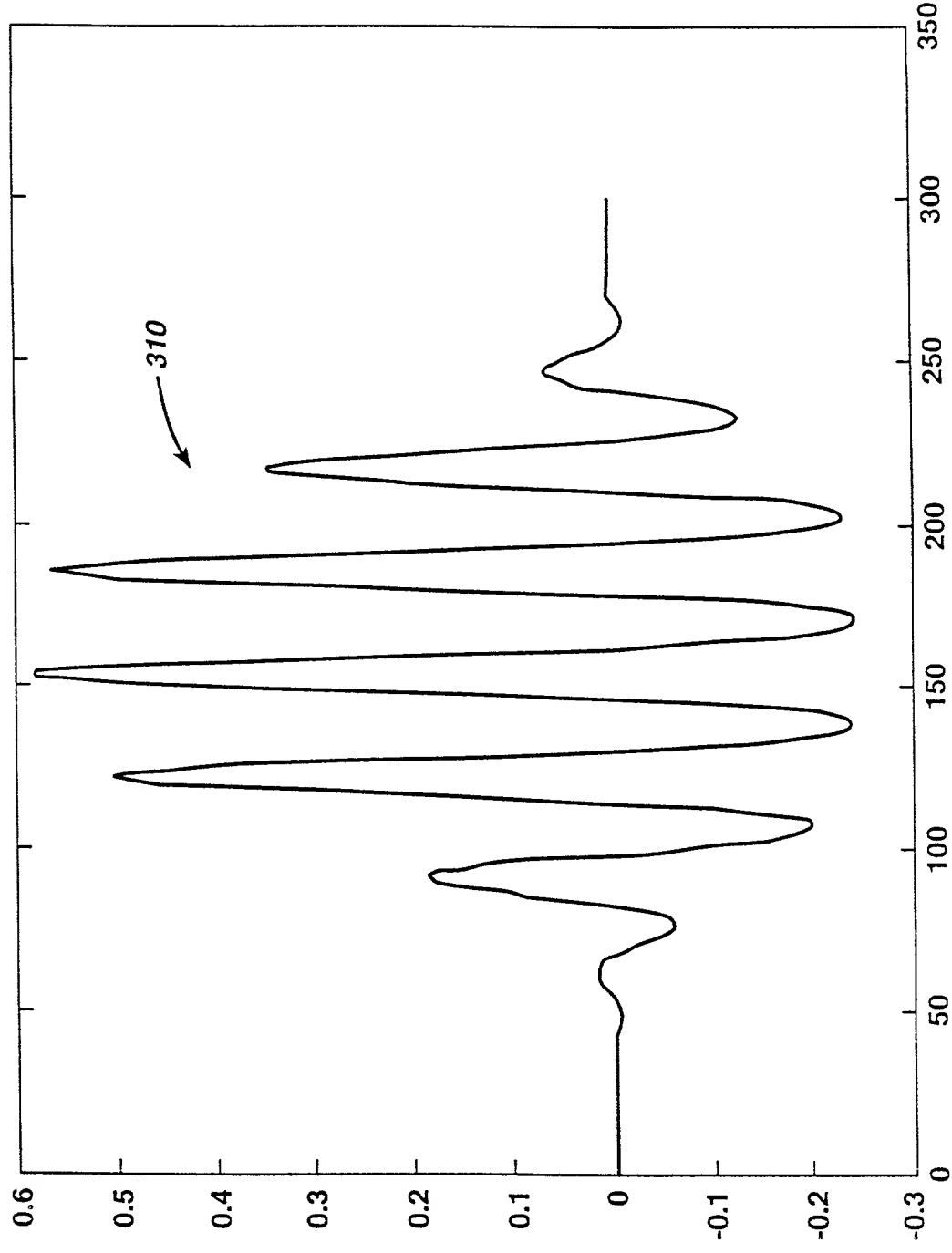
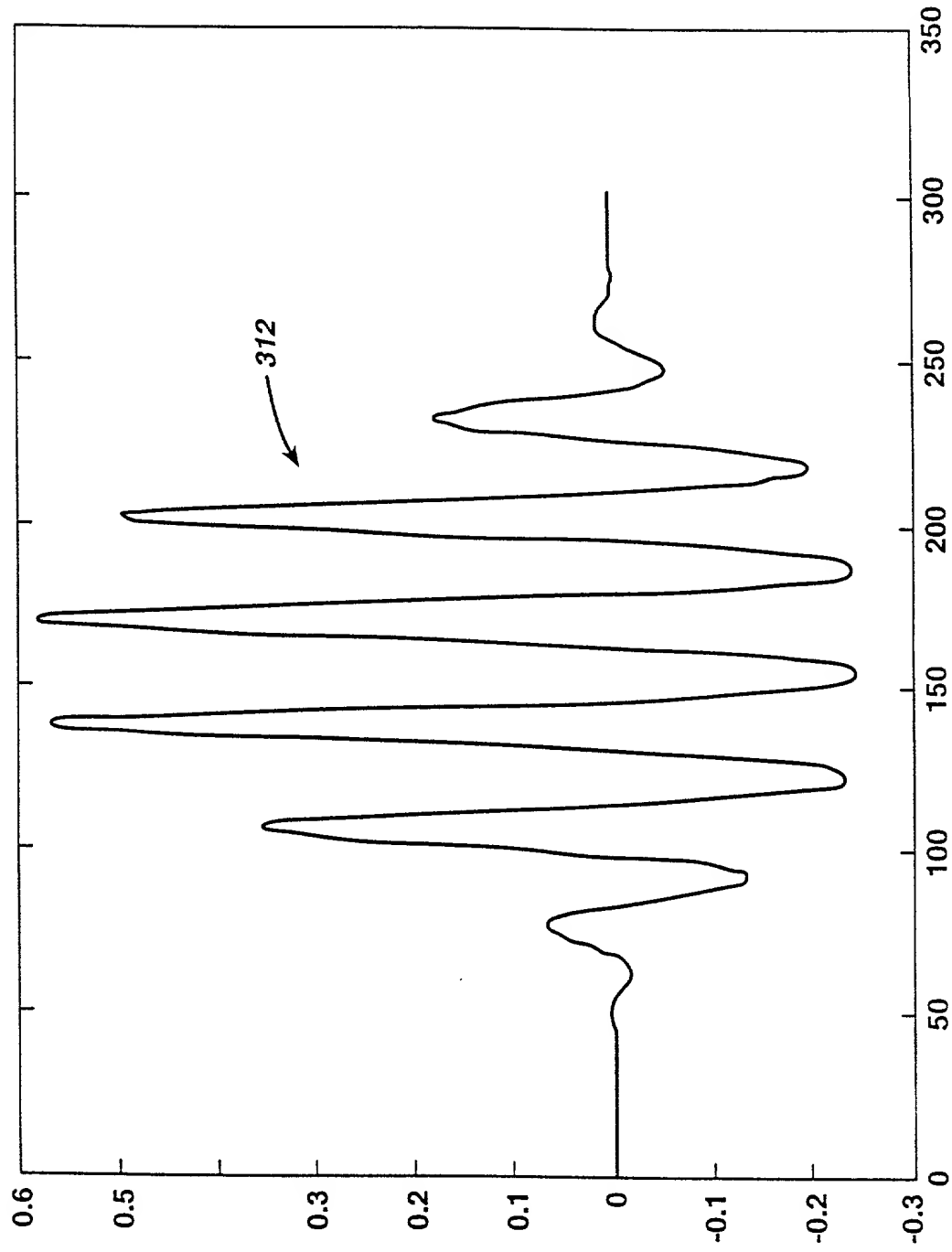


FIG. 4b

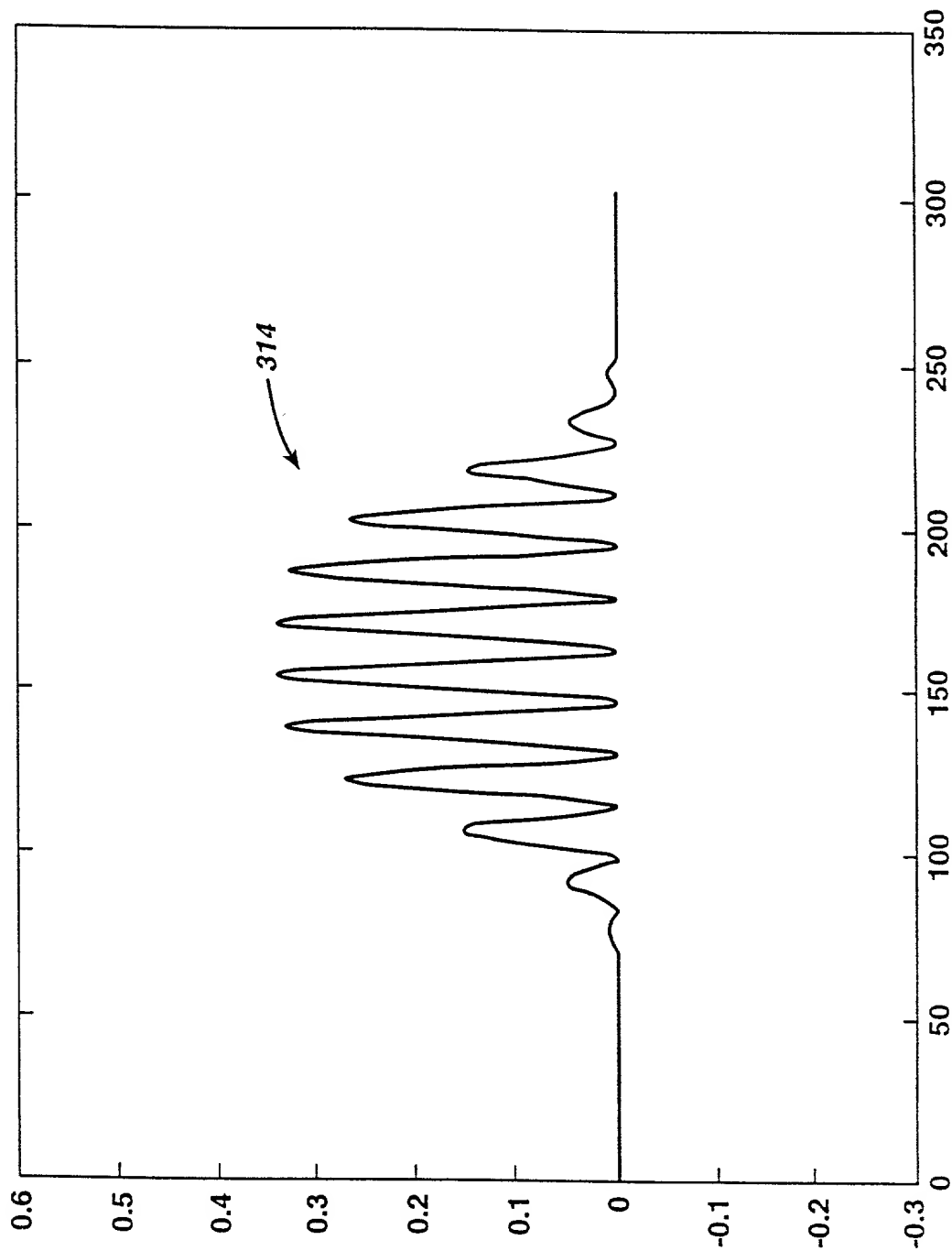
**FIG. 5a**



**FIG. 5b**



**FIG. 5c**





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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Juin-Jet Hwang et al.

Reissue Appl. Serial No.: to be assigned

Examiner:

Of Patent No.: 5,706,819

Patent Granted: January 13, 1998

Title: ULTRASONIC DIAGNOSTIC IMAGING  
WITH HARMONIC CONTRAST AGENTSHon. Commissioner of Patents  
and Trademarks  
Washington D.C. 20231REISSUE DECLARATION AND POWER OF ATTORNEY

Sir:

Juin-Jet Hwang and David Hope Simpson ("Applicants"), being all of the inventors in the above-captioned patent, hereby declare as follows:

1. Applicants hereby state that Applicants have reviewed and understand the contents of the specification, including the claims, of this reissue application and each of us believes that he is an original, first and joint inventor of the subject matter which is claimed and for which a reissue patent is sought, which is based on the disclosure of United States Letters Patent Number 5,706,819 for

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"Ultrasonic Diagnostic Imaging with Harmonic Contrast Agents" granted on January 13, 1998, and Applicants hereby solicit a reissue patent based on the same disclosure.

2. Applicants acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

3. Applicants verily believe that the above-referenced U.S. Patent No. 5,706,819 is wholly or partly inoperative or invalid by reason of the patentees claiming less than they had a right to claim in the patent. The insufficiency of the claims of the original patent are specified below. Applicants are seeking to correct this error by this broadening reissue application.

4. The error, which renders U.S. Patent No. 5,706,819 wholly or partly inoperative by reason of the patentees claiming less than they had a right to claim in the patent, results from the failure to specifically claim ultrasonic methods which use pulse sequences of three or more pulses. Such sequences are described in columns 5 and 6 of the issued patent and are the subject of newly added Claims 5-25. Such error arose through inadvertence, accident or mistake, and without any deceptive intention on the part of the Applicants.

5. We hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: W. Brinton Yorks, Jr. (Reg. #28,923), Frederick J. McKinnon (Reg. #28,240), Jack E. Haken (Reg. #26902), and Michael E. Marion (Reg. #32,266). Address all telephone calls to W. Brinton Yorks, Jr. at telephone no. (425) 487-7152. Address all correspondence to W. Brinton

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6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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